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L14	L13 with l4	26	L14
L13	l12 with l11	535	L13
L12	acetate or bicarbonate or chloride	901779	L12
L11	polycation or polylysine	8459	L11
L10	6443898.pn.	2	L10
L9	L8 same l4	16	L9
L8	L7 with l1	441	L8
L7	lung or respiratory tract	73012	L7
L6	l4 same l3	6	L6
L5	L4 with l3	0	L5
L4	dna or nucleic or plasmid	174656	L4
L3	L2 with l1	684	L3
L2	phase inversion	5995	L2
L1	polymer or micropartice or microsphere	1408782	L1

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L19	L18 and l15	4	L19
L18	L17 with l16	10	L18
L17	endosom$	2212	L17
L16	ca or calcium	2167319	L16
L15	cationic lipid or liposome or amphiphile	33884	L15
L14	L13 with l4	26	L14
L13	l12 with l11	535	L13
L12	acetate or bicarbonate or chloride	901779	L12
L11	polycation or polylysine	8459	L11
L10	6443898.pn.	2	L10
L9	L8 same l4	16	L9
L8	L7 with l1	441	L8
L7	lung or respiratory tract	73012	L7
L6	l4 same l3	6	L6
L5	L4 with l3	0	L5
L4	dna or nucleic or plasmid	174656	L4
L3	L2 with l1	684	L3
L2	phase inversion	5995	L2
L1	polymer or micropartice or microsphere	1408782	L1

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(FILE 'HOME' ENTERED AT 11:35:55 ON 06 JAN 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, CAPLUS' ENTERED AT 11:36:19 ON 06 JAN 2003

L1	3085	S	PHASE INVERSION
L2	2332642	S	POLYME? OR MICROPARTICLE
L3	1460	S	L2 AND L1
L4	2803056	S	PLASMID OR DNA OR NUCLEIC
L5	8	S	L4 AND L3
L6	5	DUP REM	L5 (3 DUPLICATES REMOVED)
L7	23974	S	POLYCATIO? OR POLYLYSINE
L8	2057893	S	ACETATE OR BICARBONATE OR CHLORIDE
L9	2069	S	L8 AND L7
L10	264	S	L9 AND L4
L11	207	DUP REM	L10 (57 DUPLICATES REMOVED)
L12	571195	S	CONDENS? OR COMPACTED
L13	32	S	L12 AND L11

L13 ANSWER 3 OF 32 MEDLINE
AN 1999422066 MEDLINE
DN 99422066 PubMed ID: 10490774
TI Transfer of YACs up to 2.3 Mb intact into human cells with polyethylenimine.
AU Marschall P; Malik N; Larin Z
CS Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DS, UK.
SO GENE THERAPY, (1999 Sep) 6 (9) 1634-7.
Journal code: 9421525. ISSN: 0969-7128.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200004
ED Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403
AB The transfer of large YAC **DNA** into human cells is a laborious procedure. High quality pulsed field gel purified **DNA** is required, which is easily sheared during manipulation before transfection or degraded in the endosome of the cell following transfection. NaCl and polyamines compact and prevent **DNA** from shearing, but may not consistently protect **DNA** after transfection. We investigated if other **polycations** such as poly-L-lysine (PLL) and polyethylenimine (PEI) could **condense** and protect large YAC **DNA** (up to 2.3 Mb) from being degraded after lipofection. **DNA condensation** was monitored by a gel retardation assay, and atomic force microscopy (AFM). **DNA** was retarded in the gel when complexed with high concentrations of PLL and PEI, indicating that **DNA** had **condensed**. However, AFM images of PLL-**DNA** complexes showed aggregates of **DNA** molecules resulting from incomplete **condensation**, whereas PEI-**DNA** complexes produced **condensed** particles approximately 30-60 nm. Exogenous PLL-**DNA** remained intact in 36% of positive clones after lipofection, whereas PEI-**DNA** was intact in 100% of positive clones. PEI is a better **condensing** reagent than PLL, protecting **DNA** from shearing and endosomal degradation, and assists in delivering YACs up to 2.3 Mb intact into human cells.

L13 ANSWER 19 OF 32 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
AN 2002-07377 BIOTECHDS
TI New compositions comprising lyophilizable and enhanced **compacted** **nucleic** acids, useful in gene therapy, particularly for facilitating treatment of pulmonary diseases, such as cystic fibrosis; gene transfer, expression in host cell, **DNA** compaction and antisense oligonucleotide for disease therapy
AU COOPER M J; KOWALCZYK T H; PASUMARTHY M K; COSTELLO M
PA COPERNICUS THERAPEUTICS INC
PI WO 2001092580 6 Dec 2001
AI WO 2000-US17499 31 May 2000
PRAI US 2001-287419 1 May 2001
DT Patent
LA English
OS WPI: 2002-090049 [12]
AB DERWENT ABSTRACT:
NOVELTY - A non-naturally occurring composition comprising unaggregated **nucleic** acid complexes, each complex consisting essentially of a single **nucleic** acid molecule and one or more **polycation** molecules having a counterion, is new. The counterion consists of **acetate**, **bicarbonate** and **chloride**.

DETAILED DESCRIPTION - A non-naturally occurring composition comprising unaggregated **nucleic** acid complexes, each complex consisting essentially of a single **nucleic** acid molecule and one or more **polycation** molecules having a counterion, is new. The counterion consists of **acetate**, **bicarbonate** and **chloride**. The complex is **compacted** to a diameter, which is less than: (a) double the theoretical diameter of a complex of the single **nucleic** acid molecule and a sufficient number of **polycation** molecules to provide a charge ratio of 1:1, in the form of a **condensed** sphere; or (b) 30 nm, whichever is larger. The **polycation** molecule has a **nucleic** acid binding moiety through which it is complexed to the **nucleic** acid, where the **nucleic** acid molecule, particularly cDNA or RNA, encodes at least one functional protein or at least one antisense **nucleic** acid. INDEPENDENT CLAIMS are also included for the following: (1) estimating the colloidal stability of a preparation of **compacted** **nucleic** acids comprising: (a) determining a turbidity parameter of a solution of **compacted** **nucleic** acid, where the turbidity parameter is defined as the slope of a straight line obtained by plotting log of apparent absorbance of light versus log of incident wavelength of the light, where the wavelength is about 330-420 nm; and (b) identifying the preparation as colloidally stable if a turbidity parameter of less than -3 is determined and identifying the preparation as colloidally unstable if a turbidity parameter of greater than or equal to -3 is determined; (2) preparing the composition by mixing the **nucleic** acid with the **polycation** having **acetate** as a counterion, at a salt concentration sufficient for compaction of the complex; (3) non-naturally occurring, soluble **compacted** complexes of a **nucleic** acid and the **polycation** molecule made by the process of (2); (4) preventing or treating a disease or other clinical condition in a subject, comprising administering intramuscularly or to the lung of the subject a prophylactic or therapeutic amount of the composition comprising the unaggregated **nucleic** acid complexes; (5) delivering polynucleotides to cells comprising contacting the composition with cells, where: (a) the **nucleic** acid is delivered to and taken up by the cells; (b) the polynucleotide encodes a protein, where the protein is expressed; and (c) the polynucleotide encodes an antisense **nucleic** acid, where the antisense **nucleic** acid is expressed.

BIOTECHNOLOGY - Preferred Composition: The **polycation**

molecules are **polylysine** or a **polylysine** derivative. Preferably, the **polylysine** derivative is **polylysine** peptide with a cysteine residue. The complex is **compacted** to a diameter of less than 90 nm, preferably less than 23 nm. Preferably, the **nucleic** acid complex is **compacted** to a diameter not more than 12 nm. The **nucleic** acid molecule comprises a promoter, which controls transcription of an RNA molecule encoding the functional protein. In particular, the protein is therapeutic. In particular, the **polycation** is CK15-60P 10 and the counterion is **acetate**, where CK15-60P10 is a polyamino acid polymer of one N-terminal cysteine and 15-60 lysine residues, and where a molecule of polyethylene glycol having an average molecular weight of 10 kDa is attached to the cysteine residue. Preferably, the **polycation** molecule comprises 30 residues of lysine and a targeting moiety. The composition is lyophilized and is rehydrated after lyophilization. Preferably, the composition does not contain a disaccharide. Preferred Method: In method (2), the mixing is monitored to detect, prevent or correct the formation of aggregated or relaxed complexes, where the salt is NaCl. The **nucleic** acid and the **polycation** are each, at the time of mixing, in a solution having a salt concentration of 0.05-1.5 M. The molar ratio of the phosphate groups of the **nucleic** acid to the positively charged groups of the **polycation** is in the range of 4:1 to 1:4. The **polycation** is added to the **nucleic** acid while vortexing at high speed or the **nucleic** acid is added to the **polycation** while vortexing at high speed. The mixing is monitored by a method consisting of electron microscopy, light scattering, circular dichroism and absorbance measurement. Preparing the composition also involves mixing a **nucleic** acid molecule with a **polycation** molecule at a salt concentration sufficient for compaction of the complex to a diameter which is less than double the theoretical minimum diameter of a complex of the single **nucleic** acid molecule and a sufficient number of **polycation** molecules to provide a charge ratio of 1:1, in the form of a **condensed** sphere, or 30 nm, whichever is larger, where unaggregated **nucleic** acid complexes are formed, where each complex consists of a single **nucleic** acid molecule and one or more **polycation** molecules. The method may also involve mixing a **nucleic** acid molecule with a **polycation** molecule in a solvent to form a complex, the mixing being performed in the absence of added salt. The **nucleic** acid forms soluble complexes with the **polycation** molecule without forming aggregates. Each complex consists essentially of a single **nucleic** acid molecule and one or more **polycation** molecules. The **polycation** has **acetate** as a counterion or where the **polycation** has a counterion consisting of **bicarbonate** and **chloride**. The **nucleic** acid complexes are preferably associated with a lipid.

ACTIVITY - Cytostatic; pulmonary. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition is useful in gene therapy, particularly for delivery of genes to animals and humans. The composition is particularly useful for treating pulmonary diseases, such as cystic fibrosis.

ADMINISTRATION - Administration may be by inhalation or intramuscular injection (claimed). Administration may also be intratracheal, intradermal, topical, subcutaneous, intrathecal, intravenous, intraperitoneal, intratumor or direct to an organ. No dosage is suggested.

EXAMPLE - Polylysines having an N-terminal cysteine and exactly 30 or 45 lysine residues (CK30 or CK45, respectively) were obtained as trifluoroacetate (TFA) salts by solid-phase synthesis. The cysteine residue was then used to conjugate polyethylene glycol (MW 10000) to form PEG-ylated polylysines CK30P10K and CK45P10K. The TFA counterion was

exchanged with **acetate, bicarbonate,** or **chloride** by gel filtration. **DNA** was **condensed** by these polylysines, dialyzed against 0.9 % NaCl, and concentrated to 1 or 4 mg/ml using centrifugal concentrators before analysis. Colloidal stability for the **DNA** complexes was determined by measuring sedimentation of **condensed DNA** during centrifugation and scattering of light (turbidity) in the wavelength range of 330-415 nm. It was found that all the tested **DNA** formulations were colloidally stable in normal saline (0.9 % NaCl) as judged by sedimentation and turbidity measurements.(71 pages)

L13 ANSWER 26 OF 32 CAPLUS COPYRIGHT 2003 ACS
AN 2000:493334 CAPLUS
DN 133:125276
TI Sustained delivery of polyionic bioactive agents
IN Levy, Robert J.
PA The Children's Hospital of Philadelphia, USA
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000041647	A1	20000720	WO 2000-US1317	20000119
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6395029	B1	20020528	US 1999-234011	19990119
PRAI	US 1999-234011	A	19990119		

AB The invention relates to compns. and methods for delivering a polyionic bioactive compn. such as a **nucleic** acid to a tissue of an animal. The compns. of the invention include compns. which comprise a matrix comprising the polyionic bioactive agent and wherein at least most of the polyionic bioactive agent at the exterior portion of the matrix is present in a **condensed** form. The invention also includes methods of making such compns., including particles, devices, bulk materials, and other objects which comprise, consist of, or are coated with such compns. Methods of delivering a polyionic bioactive agent to an animal tissue are also described. The invention further includes a method of storing a **nucleic** acid.

L13 ANSWER 28 OF 32 CAPLUS COPYRIGHT 2003 ACS
AN 2000:68361 CAPLUS
DN 132:127724
TI Chelating systems for use in the delivery of compounds to cells
IN Wolff, Jon A.
PA Mirus Corporation, USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000003738	A1	20000127	WO 1999-US16095	19990716
	W: JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1098667	A1	20010516	EP 1999-935616	19990716
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 1998-93230P	P	19980717		
	WO 1999-US16095	W	19990716		

AB Chelator contg. compds. are utilized in the delivery of mols., polymers, **nucleic** acids and genes to animal cells. At least one chelator such as crown ether is attached to a polymer and then assocd. with another polymer such as **DNA**. An ion is then added to the mixt. thereby forming **condensed DNA**. In **condensed** form and in complex with the chelator, **DNA** can be delivered to a cell. Polyacrylamidobenzo-18-crown-6 was prepd. and cation binding as well as interaction with **polylysine** and **DNA** of this crown ether was studied.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

L13 ANSWER 30 OF 32 CAPLUS COPYRIGHT 2003 ACS
AN 1998:799703 CAPLUS
DN 130:33977
TI **Compacted nucleic** acids and their delivery to cells
IN Hanson, Richard W.; Perales, Jose C.; Ferkol, Thomas W., Jr.
PA Case Western Reserve University, USA
SO U.S., 71 pp., Cont.-in-part of U.S. Ser. No. 716,415.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5844107	A	19981201	US 1996-721094	19960927
	US 6077835	A	20000620	US 1998-114475	19980713
PRAI	US 1994-216534	B2	19940323		
	US 1996-716415	A2	19960920		
	US 1996-721094	A3	19960927		

AB **Nucleic** acids are **compacted**, substantially without aggregation, to facilitate their uptake by target cells of an organism to which the **compacted** material is administered. The **nucleic** acids may achieve a clin. effect as a result of gene expression, hybridization to endogenous **nucleic** acids whose expression is undesired, or site-specific integration so that a target gene is replaced, modified or deleted. The targeting may be enhanced by means of a target cell-binding moiety. The **nucleic** acid is preferably **compacted** to a **condensed** state.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD

L13 ANSWER 31 OF 32 CAPLUS COPYRIGHT 2003 ACS
AN 1998:485169 CAPLUS
DN 129:118754
TI Method for making a compound for delivery to cells by forming a polymer in the presence of a template drug, especially **nucleic** acid
IN Wolff, Jon A.; Hagstrom, James E.; Budker, Vladimir G.; Trubetskoy, Vladimer S.; Slattum, Paul M.; Hanson, Lisa J.
PA Mirus Corp., USA
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9829541	A1	19980709	WO 1997-US24089	19971230
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6126964	A	20001003	US 1997-778657	19970103
	EP 958356	A1	19991124	EP 1997-954803	19971230
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE				
	US 2002061287	A1	20020523	US 2001-4763	20011205
	US 2002085989	A1	20020704	US 2001-5294	20011205
PRAI	US 1997-778657	A	19970103		
	US 1996-9593P	P	19960104		
	WO 1997-US24089	W	19971230		
	US 1999-464871	A3	19991216		

OS MARPAT 129:118754
AB A method of making a compd. for delivery to a cell comprising forming a polymer in the presence of a biol. active drug is disclosed.. A method of forming polymers in the presence of **nucleic** acid using template polymn. and of having the polymn. occur in heterophase systems is further disclosed. These methods can be used for the delivery of **nucleic** acids, for **condensing** the **nucleic** acid, for forming **nucleic** acid-binding polymers, for forming supramol. complexes contg. **nucleic** acid and polymer, and for forming an interpolyelectrolyte complex. The nuclear localizing peptide of SV40 T antigen was copolymd. with dithiobis[succinimidylpropionate] in the presence of **plasmid DNA** and this process enabled the formation of complexes that expressed luciferase after transfection into 3T3 cells in culture.

L13 ANSWER 32 OF 32 CAPLUS COPYRIGHT 2003 ACS
AN 1998:323163 CAPLUS
DN 128:326554
TI Carrier vehicles for delivery of **nucleic** acid material to target cells in biological systems
IN Schacht, Etienne Honore; Seymour, Leonard Charles William; Ulbrich, Karel
PA Schacht, Etienne Honore, Belg.; Seymour, Leonard Charles William; Ulbrich, Karel
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9819710	A2	19980514	WO 1997-GB2965	19971106
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9748739	A1	19980529	AU 1997-48739	19971106
	AU 740747	B2	20011115		
	EP 941123	A2	19990915	EP 1997-911324	19971106
	EP 941123	B1	20020612		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	AT 218891	E	20020615	AT 1997-911324	19971106
	US 6312727	B1	20011106	US 1999-306568	19990506
PRAI	GB 1996-23051	A	19961106		
	WO 1997-GB2965	W	19971106		

AB Synthetic polymer-based carrier vehicles for delivery of **nucleic** acid material to target cells in biol. systems are made by self-assembly of the **nucleic** acid with a cationic polymer material so as to **condense** the **nucleic** acid and form a polyelectrolyte complex. This complex is then treated with a reactive hydrophilic polymer material which grafts to the complex forming a hydrophilic coating that stabilizes the complex and provides an outer protective steric shield. These carrier vehicles can be useful in gene therapy. Thus, an aq. soln. of poly(L-lysine) was added to a **DNA** soln. at a final cation to anion ratio 2 and allowed to stand for .gtoreq.30 min at room temp. to permit complete self-assembly of the complexes. Then, methacryloyl-terminated glycine-phenylalanine-leucine-glycine p-nitrophenyl ester copolymer with N-2-hydroxypropylmethacrylamide was grafted onto the poly(L-lysine)-**DNA** complex to provide an outer protective steric shield and to stabilize the complex. The max. concn. of **DNA** depended on the hydrophilicity of the structure of the cationic polymer. Typical particles were discrete and had diam. 30-50 nm. The coated complexes were relatively stable and easy to handle.